REMARKS

The Specification has been reviewed and all spelling, TRADEMARKS, and like errors have been corrected by the amendments set forth above. In addition, as requested by the Examiner, the specification has been amended to include the current address of the ATCC.

Claims 1, 4-5 and 7-13 are currently pending in the application. Claim 3 has been withdrawn as being drawn to a non-elected invention, and claims 2 and 6 have been canceled. Claims 1 and 5 have been amended. Support for these amendments can be found throughout the specification and claims as originally filed.

Accordingly, no new matter has been added by the current amendments. Moreover, the claim amendments requested herein should in no way be construed as acquiescence to any of the rejections and have been made solely to expedite prosecution of the application. Applicants reserve the right to pursue the claims as originally filed and/or prior to amendments made herein in this or a separate application(s).

Rejections under 35 U.S.C. §112, First Paragraph

Claims 1, 2 and 4-13 have been rejected on the ground that the specification does not contain a written description of the claimed invention. Specifically, the Office Action states that

> The instant claims do not provide sufficient structural and functional characteristics coupled with a known or disclosed correlation between function and structure. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus of "B7 molecules", the specification does not provide sufficient written description forth the genus of "B7 molecules" targeted by the current claims. (Paper No. 9, page 4).

Claims 1, 2 and 4-13 were further rejected on the ground that the specification, "while enabling for certain known B7 molecules, including B7-1, B7-2, B7RP-1 and B7h . . . does not reasonably provide enablement for 'any B7 molecule(s)'. (Paper No. 9, page 5).

Applicants respectfully traverse these rejections. However, solely in the interest of expediting prosecution, the claims have now been amended to provide that the B7

molecule is selected from the group consisting of B7-1, B7-2, B7RP-1 and B7h. Accordingly, these rejections are now moot. Notwithstanding, Applicants maintain that the specification provides sufficient guidance for one of ordinary skill in the art to make and use other B7 molecules without undue experimentation. The amino acid and nucleotide sequences of a number of representative species of B7 molecules are provided. Further, functional characteristics of these molecules (for example induction of proliferation and IL-2 secretion, and avidity for CTLA4, or in the case of a blocking variant, the ability to block, e.g., B7-1 or B7-2 costimulation) are also provided, and may be combined with the structural characteristics provided to demonstrate that Applicants were in possession of the genus of B7 molecules at the time of filing. Moreover, the specification teaches a representative number of antibodies which specifically bind either B7 molecules (for example, see page 50, line 2-7, page 86, line 37; and Table VIII). The field of antibody generation is mature and the knowledge and level of skill in the art is high, thus the combination of this disclosed information is sufficient to indicate to one of skill in the art that Applicants were in possession of the necessary common attributes or features of the elements possessed by the members of the genus of antibodies specific for B7 molecules.

Rejections under 35 U.S.C. §103(a)

Claims 1, 2, and 4-12 have been rejected as obvious over Co *et al.* (US 2002/0176855 A1) in view of DeBoer *et al.* (US Patent No. 5,747,034), Cottens *et al.*, (WO 95/16691), and Strom *et al.*, (Therapeutic Immunology, Austen *et al.*, (Ed.) Blackwell Science, Cambridge, MA 1996). More specifically, the Office Action states:

> Given the teachings of the prior art to combine anti-B7-1 and anti-B7 antibodies alone or in combination with other immunosuppressive therapy to inhibit immune responses, including therapeutic regimens of treating SLE alone in conjunction with the know use of rapamycin to treat SLE alone or in combination with other immunosuppressive antibodies, including anti-B7 antibodies; one of ordinary skill in the art at the time the invention was made would have been motivated to combine anti-B7-1 and anti-B7-2 antibodies with rapamycin to inhibit immune responses in various therapeutic regiments including the treatment of SLE at the time the invention was made. The various dosing regiments encompasses by the instant claims were obvious at the time the invention was made, given that it was well known an practice[d] at the time the invention was made

> to provide immunosuppressive therapy based upon the condition and needs of the patient, as evidenced by the teachings of the prior art. (Paper No. 9, page 9).

Applicants respectfully traverse this rejection. Co, *et al.* teach methods of inhibiting an immune response by administering a combination of B7-1 and B7-2 antibodies. However, while Co, *et al.* do generally suggest that other "standard therapy drugs" may also be administered with these antibodies, they provide absolutely no evidence that the co-administration of additional drugs could be advantageous. Thus, this suggestion amounts to merely an unguided and speculative invitation to further experimentation, which is not the standard by which obviousness under 35 U.S. C. §103 is determined. Moreover, Co *et al.* do not teach, or even suggest, that rapamycin should be considered a "standard therapy drug." Indeed, the very absence of rapamycin in the list of examples provided by Co *et al.* clearly implies that, as experts in the field, they did not even consider using rapamycin in combination with B7 antibodies. Therefore, Applicants respectfully submit that Co *et al.* actually teach away from the presently claimed invention..

While Co *et al.* teach that a combination of B7-1 and B7-2 antibodies is a more effective inhibitor of T cell proliferation than either antibody alone, DeBoer, *et al.* teach that co-administration of a B7-1 antibody with cyclosporinA (CsA) successfully inhibits T cell proliferation *in the absence of blocking agents for B7-2* (e.g., see column 28, lines 22-28). DeBoer *et al.* explain this unexpected finding by noting that,

> "This may be explained by the fact that signal transduction after cross-linking with CD28 results in two independent signaling pathways, one being CsA-sensitive and one being CsA-insensitive. It may be that signal transduction after interaction of CD28 with B7-2 is mediated by the CsA-sensitive pathway." (column 6, lines 27-33).

Accordingly, Applicants respectfully submit that one of ordinary skill in the art would conclude from the teachings of DeBoer *et al.* alone, or in combination with Co *et al.*, that CsA can be used in combination with B7-1 antibodies as a *substitute* for B7-2 antibodies, and would not have been motivated to use a combination of B7-1 and B7-2 antibodies with CsA, let alone any other immunosuppressive drug.

Moreover, while DeBoer *et al.* suggest that other immunosuppressive agents, including rapamycin, might be used in combination with B7-1 antibodies, they fail to provide any teaching whatsoever that any of these other immunosuppressive agents would be as effective as CsA. For example, CsA and rapamycin are not equivalent molecules, and do not act via the same biological pathways (e.g., see Strom *et al*, Figure and Table 36.1). Indeed, one of ordinary skill in the art, when presented with the teachings of DeBoer *et al.* and/or Co *et al.* in their entirety would not have been able to reasonably predict that the combination of anti-B7-1 antibodies and rapamycin would yield the same immunological response as the combination of anti-B7-1 antibodies and CsA. Nor would the skilled artisan have been able to reasonably predict that that the combination of rapamycin, B7-1 antibodies *and B7-2* antibodies would result in an increased level of survival in a clinically relevant animal model when compared to the level of survival in animals treated only with B7-1 and B7-2 antibodies as demonstrated by Applicants (see Examples 2 and 3).

Cottens *et al.* and Strom *et al.* alone or in combination do not cure the deficiencies of Co *et al.* and DeBoer *et al.*. Cottons *et al.* teach the use of rapamycin as an immunosuppressant, and generally suggest that rapamycin might be used in combination with other immunosuppressive drugs or immunosuppressive monoclonal antibodies. Strom *et al.* generally teach a multi-tiered approach to immunosuppressive therapy. Strom *et al.* further disclose that the majority of basic protocols involve a combination of CsA or Fk506 plus corticosteroids with or without azathioprine, and suggest that anti-lymphocyte globulin or OKT3 might also added to reduce the dose of CsA required (page 454). Thus, while Strom *et al.* do include rapamycin in their general description of immunosuppressants, they do not actually teach or suggest the use of rapamycin in any multi-tiered immunosuppressive therapy regimen.

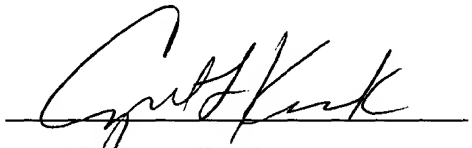
In short, none of the cited references alone or in combination suggest the use of a combination of rapamycin with at least two B7 antibodies as presently claimed. At best, the cited references might be viewed as providing the suggestion to try various combinations of immunosuppressive antibodies and immunosuppressive agents. However, this is not the standard required to establish obviousness under 35 U.S.C. §103.

Accordingly, Applicants respectfully submit that a *prima facie* case of obviousness has not been established, and reconsideration and withdrawal of this rejection is requested.

SUMMARY

In view of the remarks set forth above, it is respectfully submitted that this application is in condition for allowance. It there are any remaining issues or the Examiner believes that a telephone conversation with Applicants' attorney would expedite the prosecution of the above-identified application, the examiner is urged to call Applicant's attorney at (617) 227-7400.

Respectfully submitted,
LAHIVE & COCKFIELD, LLP



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